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Medication Development of Ibogaine as a Pharmacotherapy for Drug Dependence^a

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ABSTRACT: The potential for deriving new psychotherapeutic medications from natural sources has led to renewed interest in rain forest plants as a source of lead compounds for the development of antiaddiction medications. Ibogaine is an indole alkaloid found in the roots of *Tabernanthe iboga* (Apocynaceae family), a rain forest shrub that is native to equatorial Africa. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger and in higher doses as a sacrament in religious rituals. Members of American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from addictive substances, including psychostimulants and cocaine. Anecdotal reports attest that a single dose of ibogaine eliminates withdrawal symptoms and reduces drug cravings for extended periods of time. The purported antiaddictive properties of ibogaine require rigorous validation in humans. We have initiated a rising tolerance study using single administration to assess the safety of ibogaine for the treatment of cocaine dependency. The primary objectives of the study are to determine safety, pharmacokinetics and dose effects, and to identify relevant parameters of efficacy in cocaine-dependent patients. Pharmacokinetic and pharmacodynamic characteristics of ibogaine in humans are assessed by analyzing the concentration-time data of ibogaine and its desmethyl metabolite (noribogaine) from the Phase I trial, and by conducting *in vitro* experiments to elucidate the specific disposition processes involved in the metabolism of both parent drug and metabolite. The development of clinical safety studies of ibogaine in humans will help to determine whether there is a rationale for conducting efficacy trials in the future.

INTRODUCTION

The potential for deriving new psychotherapeutic medications from natural sources has led to renewed interest in rain forest plants for the development of anti-addiction medications. Ibogaine is an indole alkaloid found in the root bark of *Tabernanthe iboga* (Apocynaceae family), a shrub that grows in West Central Africa. The Pygmies attribute the discovery of the plant to the warthogs who it seems are very fond of it.¹ Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger and thirst, and in high doses for its psychoactive properties as a sacrament in religious rituals. Discussion of the central nervous system (CNS) and cardiovascular actions of ibogaine have appeared in the literature since the early 1900s.² In the 1950s, CIBA investigated

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ibogaine as an antihypertensive agent, but these studies were not continued because the company was unconvinced of its commercial potential. The pharmacology of ibogaine was studied extensively by the French pharmacologists Lambert, Heckel and Pouchet early in the 20th century (for review, see Ref. 3). After the introduction of the Rauwolfia and given the general interest in the Apocynaceae family of which *Tabernanthe iboga* is a member, French scientists pursued chemical, pharmacological and behavioral studies of ibogaine.⁴⁻⁶ Ibogaine was marketed in France under the tradename Lambarene until 1970.⁷

The putative antiaddictive properties of ibogaine were first described by Howard Lotsof.⁸ He reported that ibogaine administrations led to an active period of visualizations that were described as a "waking dream state," followed by an intense cognitive phase of "deep introspection." Drug-dependent individuals who had received ibogaine treatments reported that the visions usually centered on early childhood and other significant developmental events that occurred during formative periods of their life. In the cognitive phase, insights were gained into their addictive and self-destructive behaviors. Interestingly, at the end of the ibogaine treatment sessions, opiate- and cocaine-dependent subjects reported an alleviation or in some cases a complete cessation of drug 'craving' for extended periods of time, and a few patients remained drug-free for several years thereafter. Opiate-dependent patients reported that ibogaine blocked the symptoms of opiate withdrawal. An informal self-help network had provided ibogaine treatments from 1987 until 1993 to addicts in Europe⁹ (International Coalition of Addict Self Help, ICASH). Based on his own experience and that of six of his friends, Howard Lotsof filed a series of use patents describing a method for treating narcotic, psychostimulant, nicotine, alcohol and polydrug dependence with ibogaine (US Patents 4,499,096; 4,587,243; 4,857,523). Our research team at the University of Miami were the first to request permission from the US Food and Drug Administration (FDA) to conduct a limited Phase I Pharmacokinetic and Safety Trial in male subjects (IND 39,680). This clinical protocol was initially limited to include only ibogaine veterans. In April 1995, the FDA approved a revised clinical protocol to conduct these studies in cocaine-dependent male volunteers. However, these dose-escalation studies have not progressed beyond 2 mg/kg oral doses due to a lack of research support for the clinical trial.

The anecdotal reports of ibogaine's purported efficacy require controlled clinical studies in order to validate the claims that either single or repeated ibogaine administrations are effective for treating substance abuse. However, ibogaine's actions may have specific pharmacological actions that target an underlying neurochemical etiology and/or neural adaptations associated with chronic cocaine or opiate abuse, along with the individual psychosocial disorders as discussed above. As with most pharmacological agents, it is important for ibogaine pharmacotherapy to be integrated with psychotherapy. This suggestion for drug development of ibogaine as a pharmacotherapy for substance abuse is consistent with the current advances in substance abuse treatment strategies, which indicate that outcomes can be enhanced and extended by combining the most effective forms of psychotherapy and pharmacotherapy.¹⁰

PROOF-OF-CONCEPT IN ANIMAL BEHAVIORAL MODELS

Ibogaine is reportedly not a substitute for narcotics or stimulants, it is not addicting, and it promotes long-term drug abstinence after a single-dose administration. The narrative claims of humans who were successfully treated with ibogaine have led to investigations in rodents and monkeys. Ibogaine administrations have been shown to reduce morphine self-administration^{11,12} and decrease morphine-induced locomotor ac-

months. Ibogaine had been administered to opiate and cocaine addicts in Europe and Central America through an informal self-help network.⁹ Although promising, these anecdotal reports from addict self-help groups have not been verified in controlled clinical trials by established investigators. Although the precise neurochemical mechanism(s) of action for ibogaine have only begun to be studied, it is important to emphasize that many therapeutic successes have arisen empirically. The anecdotal reports of the effectiveness of ibogaine for the treatment of opioid and cocaine dependence provide a basis for further studies of ibogaine as a pharmacotherapy for drug dependence.

SAFETY CONSIDERATIONS

Ibogaine has a variety of dose-dependent pharmacological actions that may not be relevant to its effectiveness for opiate detoxification and psychostimulant and opiate dependence, but may influence considerations for safety. However, toxicological studies conducted in primates have demonstrated that oral ibogaine administrations, given at doses ($5 \times 25 \text{ mg kg}^{-1}$) recommended for the treatment of cocaine and opiate dependence, appear to be safe and free of behavioral or cerebellar toxicity.⁶⁰ The development of ibogaine as an antiaddiction drug has been hindered due to uncertainties over potential cerebellar neurotoxicity demonstrated in rat studies.^{61,62} O'Hearn and Molliver⁶¹ showed that high doses of ibogaine (100 mg kg^{-1} or $3 \times 100 \text{ mg kg}^{-1}$) causes degeneration of the cerebellar purkinje cells in rats. Molinari *et al.*⁶³ reevaluated the dose effects of ibogaine. In this study, a lower dose (40 mg/kg) of ibogaine, one effective in reducing morphine and cocaine self-administration, displayed no degeneration above the level seen in saline-treated controls. These observations suggested that the degenerative and 'antiaddictive' properties of ibogaine reflect different actions of the drug.

Although the Phase I investigations by our group have not advanced recently, we have had the opportunity to obtain additional safety data in persons receiving ibogaine treatments abroad under controlled conditions. Baseline screening in these subjects included a medical evaluation, physical examination, electrocardiogram (ECG), blood chemistries, and hematological workup, as well as psychiatric and chemical dependency evaluations. A total of thirty (23 male, 7 female) drug-dependent subjects were assigned to one of three fixed-dose treatments under open label conditions: 500 mg, 600 mg, and 800 mg ibogaine. Adverse effects were assessed by clinician side-effect ratings and open-ended query. No significant adverse events were seen under these study conditions. The most frequent side effects observed were nausea and mild tremor at early time points after drug administration. Random regression of vital signs (respiration rate, systolic and diastolic blood pressures and pulse) revealed no significant changes across time or by treatment condition. White blood cell count, neutrophil levels, sodium or potassium levels were in the normal range. No significant changes from baseline were seen for alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) alkaline phosphatase (ALP), and γ -glutamyl transpeptidase (GGT). Intensive cardiac monitoring demonstrated that no electrocardiographic abnormalities were produced or exaggerated following ibogaine administration. These preliminary results demonstrate that single oral doses of ibogaine were well tolerated in drug-dependent subjects, and that there were no significant problems with safety within this dose range.

Concern over potential cerebellar toxicity⁶¹ compelled us to examine ibogaine's effects on postural stability, body tremor and appendicular tremor (FIG. 4). In the FDA pharmacokinetic and safety trial studies, two doses of ibogaine (1 and 2 mg kg^{-1}) were administered to 9 volunteers with histories of recent cocaine abuse. Static posturogra-

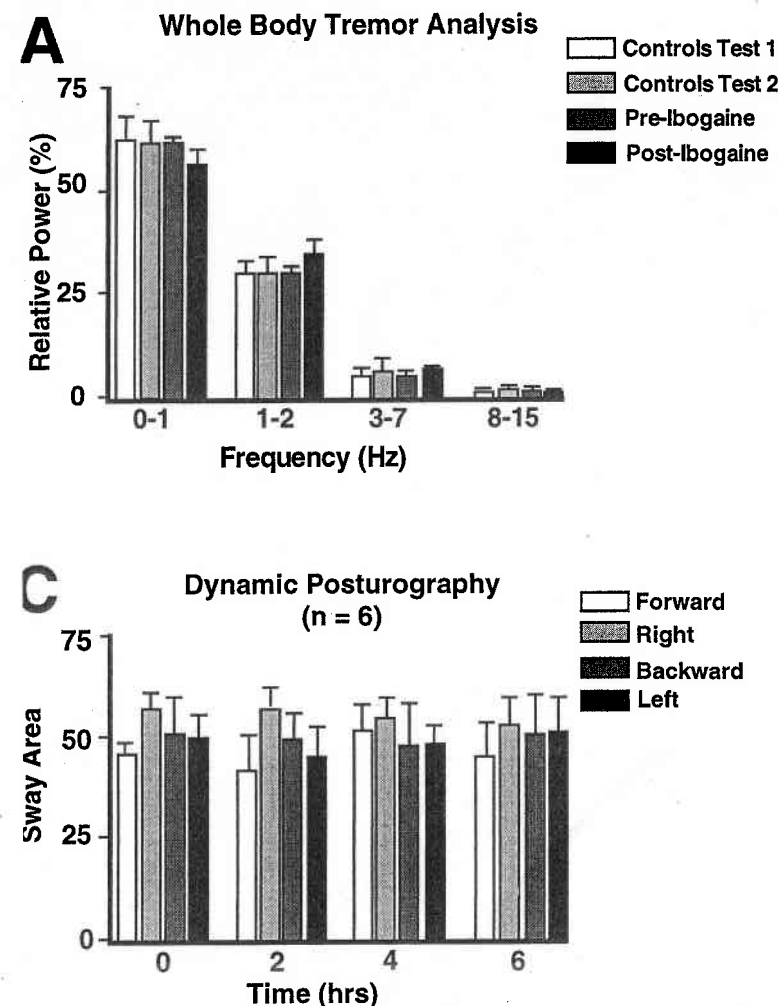


FIGURE 4. (A) 'Whole body tremor' analysis on NeuroCom platform. Mean relative power of involuntary movement expressed in 4 frequency bands. Normal age-matched and drug-free patient volunteers ($n = 15$) were tested at two different times (test and retest validation) and compared with patients ($n = 6$) tested before and 48 hr after an oral dose of ibogaine (2 mg kg^{-1}). (B) 'Static posturography' analysis on portable platform. Mean sway area for six subjects as a function of time after ingestion of 2 mg kg^{-1} dose of ibogaine. Sway area is determined by measuring actual area of shifts of center of gravity as subject stands on the force plate; the actual height and weight of the subject are expressed as $(1 - [\text{actual area} - \text{theoretical area}]) \times 100\%$. One hundred percent represents the best score (*i.e.*, no shifting of weight beyond the theoretical limit). (C) 'Dynamic posturography' analysis on portable platform. Mean sway area as a function of time after 2 mg kg^{-1} dose of ibogaine. Area of purposeful sway is based on measuring actual area of shifts of center of gravity as the subject purposefully shifts his weight to intersect the target arc. $(1 - [\text{actual areas covered} - \text{theoretical area within limit of stability}]) \times 100$. (D) Extended hand tremor analysis by accelerometer ($n = 6$). The mean relative power of movement as a function of time after ibogaine administration. Bars are shaded to represent the frequency (Hz) separated into 4 bands.

tivity.¹³ Ibogaine eliminates some of the signs of opiate withdrawal precipitated by naloxone or naltrexone in morphine-dependent rats^{14,11} and monkeys.¹⁵ However, Sharpe and Jaffe¹⁶ failed to demonstrate significant effects of ibogaine administrations on the signs of morphine-withdrawal in mice at either subtremerogenic (5 and 10 mg/kg subcutaneous (s.c.)) or tremorogenic (20 and 40 mg/kg s.c.) ibogaine doses. In the single-dose suppression test in monkeys, ibogaine reduced the total number of withdrawal signs, but failed to substitute completely for morphine (College on the Problems of Drug Dependence (CPDD) Drug Testing Program, 1989). Dzoljic *et al.*¹⁴ reported that ibogaine administered intracerebroventricularly at 4–16 µg/kg attenuated the naloxone-precipitated withdrawal syndrome in chronic morphine-dependent male rats. In this study, ibogaine had more consistent effects on withdrawal signs that were related to locomotor behavior. Luxton *et al.*¹⁷ using the place conditioning procedure showed that 40 mg/kg i.p. ibogaine reduced the rewarding effect of a single injection of morphine (2 mg/kg i.p.) in rats. The attenuation of the effect of morphine was seen even if the animals were pretreated with opiate 24 hr before the test. After the fourth morphine conditioning trial, ibogaine failed to modify the reward of morphine. Ibogaine by itself was neither reinforcing nor aversive, and it did not affect place conditioning motivated by drugs that are not rewarding.¹⁸

Cocaine-induced stimulation of locomotor activity was decreased by ibogaine in mice¹⁹ and rats.²⁰ Ibogaine administrations also reduced cocaine intake in mice²¹ and rats.^{22,12} In mice, cocaine intake was reduced sharply by ibogaine administrations at doses of 40 mg/kg i.p.¹⁹ However, Dworkin *et al.*²³ failed to demonstrate significant effects of ibogaine on cocaine self-administration in rats, but did show sensitive effects of ibogaine on responding maintained by heroin. In contrast to this work, cocaine self-administration was reportedly decreased for up to 48 hr after a single ibogaine dose in rats.²² Repeated administration of ibogaine on three consecutive days produced a significant and marked decrease in cocaine intake in this study. Glick *et al.*¹² have reported reductions in cocaine self-administrations in rats that persisted for several days following three doses of ibogaine. The long-lasting *aftereffects* in rats and humans have led to the suggestion that ibogaine may persist in brain or that an active metabolite with a slow clearance rate may contribute to the actions of ibogaine. However, studies in rhesus monkeys demonstrated that dose-effect curves for ibogaine's effects on food- and cocaine-maintained behavior in individual monkeys did not show consistent dose dependency for either event.²⁴ While questions have been raised previously concerning the use of different chemical preparations of ibogaine across earlier studies,²⁵ one possible explanation for conflicting results is species or strain differences in the patterns of ibogaine metabolism and clearance rates.²⁶ For example, ibogaine is cleared from blood very rapidly in the primate as compared to either the rat or human subjects.^{26,27}

Glick and co-workers¹² have described the effects of iboga alkaloids on extracellular levels of dopamine and its metabolites in the nucleus accumbens and striatum. Morphine and cocaine intake were dose-dependently decreased (2.5 to 80 mg/kg i.p.) in the hour after treatment. Some, but not all of the alkaloids (ibogaine, tabernanthine, desethylcoronaridine, and the R-isomer of ibogamine) reduced drug intake the day after they were administered. Interestingly, R-ibogamine produced the most consistent and persistent pattern of *aftereffects* showing decreased drug intake following two or three injections. At the doses used to assess effects on drug intake, most of the alkaloids were tremorogenic, while R-ibogamine and R-coronaridine induced very weak or no tremors. Using *in vivo* microdialysis, the effects of R- and S-enantiomers were compared for their effects on extracellular dopamine levels in the striatum and nucleus accumbens. The R-enantiomers decreased dopamine levels in both brain regions, while the S-enantiomer failed to produce a significant effect. These results indicate

that the putative 'antiaddictive' and tremorogenic effects of iboga alkaloids can be dissociated.

IDENTIFICATION OF A PRIMARY METABOLITE

The narrative reports of long-lasting effects in humans after a single dose, together with the demonstrated *aftereffects* of ibogaine on drug self-administration in rodents, have led to the suggestion that ibogaine may persist in the body or that there may be one or more active metabolites formed.^{28,22} We have developed a procedure for quantifying ibogaine and have identified a single primary metabolite in blood samples from rats, primates and humans.^{29,30} Our group was the first to identify the primary metabolite as 12-hydroxyibogamine (noribogaine), by full scan electron impact gas chromatography/mass spectrometry (GC/MS). The analytical procedure involved a solvent extraction under basic conditions with D₃-ibogaine as an internal standard. Urines taken from dosed monkeys and humans were extracted under strongly basic conditions (pH >10) with ethyl acetate. Extracts were evaporated to dryness, reconstituted with methanol, and analyzed by GC/MS in full scan electron impact ionization mode. Analysis of the resulting total-ion chromatograms revealed a peak identified as parent drug, ibogaine, by comparison with an authentic standard. In addition, all samples were found to contain a second major component eluting after ibogaine. Similar spectral characteristics of this peak to ibogaine's spectrum (*i.e.*, presence of M/Z 122, 135, 136 and 149 fragments) define it as an ibogaine metabolite (FIG. 1). The apparent molecular ion at M/Z 296 suggests that it is formed by a loss of a methyl group. In addition, the appearance of a fragment of mass 211 in place of the M/Z 225 fragment of the ibogaine spectrum indicates that the demethylation occurs on the indole end of the molecule. The most probable site for metabolic demethylation of ibogaine was the methoxy group, resulting in the compound 12-hydroxyibogamine (noribogaine). To confirm the identity of the desmethyl metabolite, an authentic standard of noribogaine (s.a. Omnicem, Belgium) was run in parallel with the experimental samples. This analysis of the authentic noribogaine standard gave a single peak at the same retention time and with the same electron impact fragmentation pattern as the endogenous compound isolated from monkey and human urines.^{26,30}

Limited pharmacokinetic measurements have been obtained from human patient volunteers who had received single oral doses of ibogaine. The results have provided some important information about the metabolism and clearance of ibogaine. At 4 hr, the peak concentrations of ibogaine measured in blood ranged from 600 to 1250 ng/ml in two male subjects who had received 600 mg and 800 mg, respectively (FIG. 2). The time required to eliminate the majority of absorbed ibogaine (>90%) was 24 hr post-dose (FIG. 2). The pharmacokinetic profiles determined in whole blood demonstrate that the concentrations of 12-hydroxyibogamine (noribogaine) measured at 24 hr remained elevated in agreement with previous findings.³⁰ The concentration of noribogaine measured at 24 hr postdose was in the range of 800 ng/ml. One female opiate-dependent subject treated with a single 500-mg oral dose of ibogaine had very low levels of ibogaine measured in blood (FIG. 2C). However, the peak levels of the metabolite were comparable to those seen in the male subjects that had received higher doses of ibogaine. Interestingly, in contrast to the two male subjects who had elevated levels of ibogaine measured in blood, this female subject reported no remarkable 'visionary' experience at this dose of ibogaine. Physical dependence to opiates is characterized by a distinctive pattern of signs and symptoms that make up the withdrawal syndrome. Physician-rated assessments demonstrated that there were no objective signs of opiate withdrawal seen in this female subject. These preliminary observations further suggest

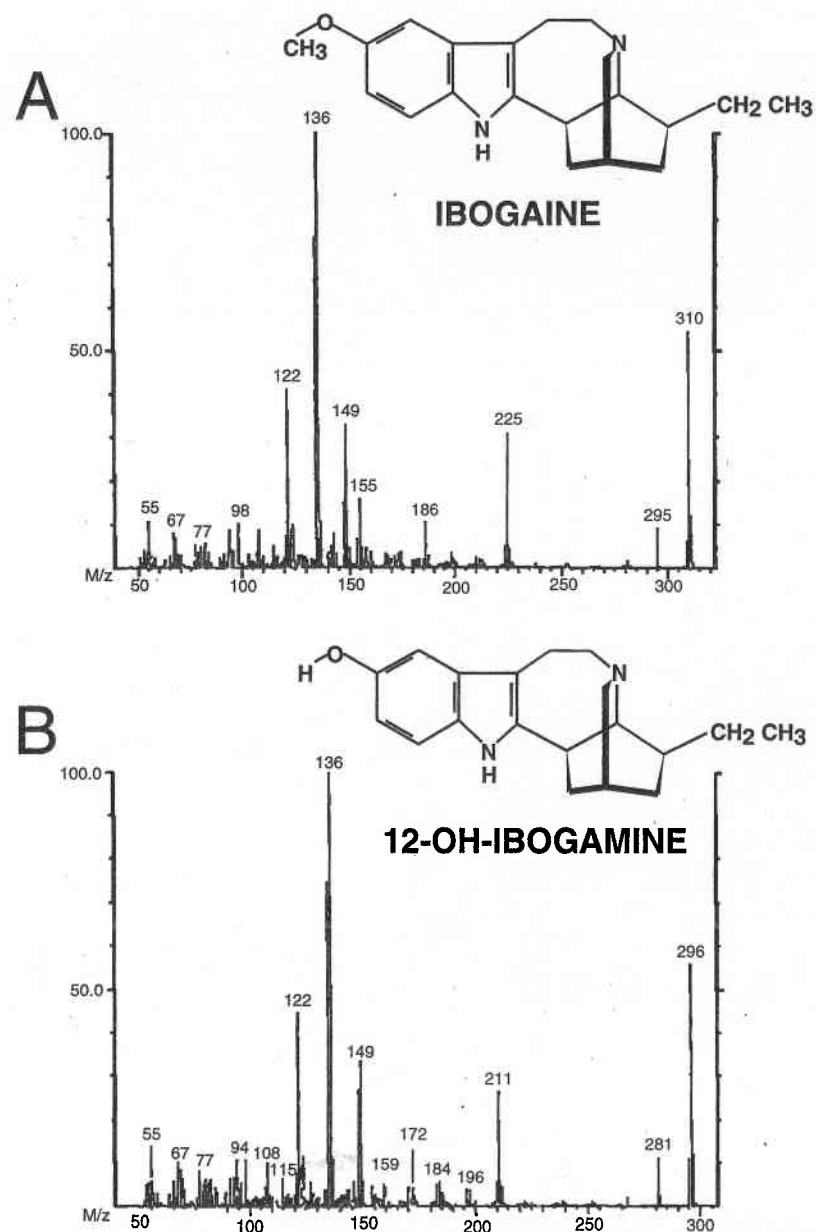


FIGURE 1. Identification of an ibogaine metabolite in human urine. Full scan electron impact mass spectra of (A) ibogaine and (B) 12-hydroxyibogamine propyl ether derivative.

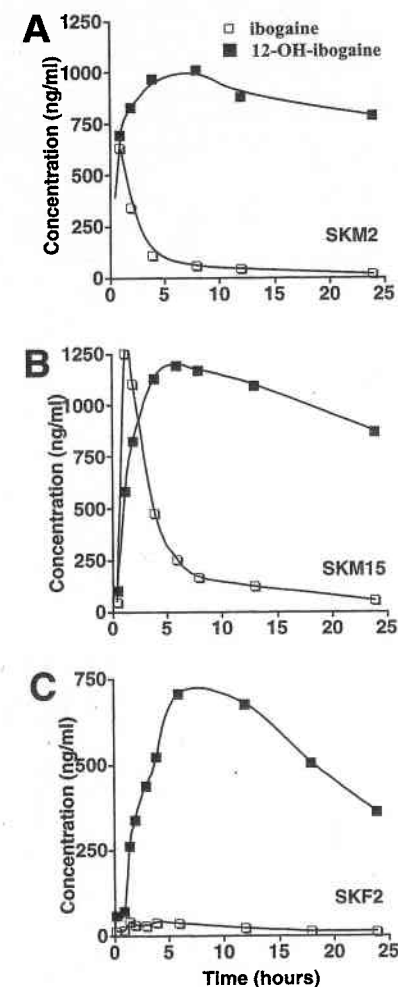


FIGURE 2. Pharmacokinetics of ibogaine and noribogaine over the first 24 hr after oral doses in human subjects. Data shown are from representative male and female subjects. Values for parent drug and the desmethyl metabolite were measured in whole blood samples at the times indicated. Demographic information for the subjects codes are as follows: SKM2 (W/M 39 yr, 800 mg); SKM15 (W/M 46 yr, 1000 mg); SKF2 (W/F 30 yr, 500 mg). Abbreviations: SK, St. Kitts.

that the action of the metabolite may account in part for ibogaine's ability to reduce the symptoms of spontaneous withdrawal in opiate-dependent humans.

IDENTIFYING MULTI-SITE TARGETS AND MECHANISM(S) OF ACTION

The concentrations of ibogaine and noribogaine have been measured in rat brain following oral and intraperitoneal administrations.^{27,31} The significance of micromolar interactions of ibogaine and noribogaine with various radioligand binding sites was related to the concentration of parent drug and metabolite in brain. Regional brain levels of ibogaine and noribogaine were measured in rat cerebral cortex, striatum, brainstem and cerebellum at 15 min, and 1 and 2 hr post drug administration. The results demonstrate that ibogaine is rapidly detected in brain following oral administration.²⁷ The metabolite was detected at the earliest time point (15 min), consistent with first pass metabolism of the parent drug.²⁶ Administration of ibogaine (50 mg/kg per os (p.o.)) in rodents resulted in levels of ibogaine and noribogaine ranging from 4 to 17 μ M and 1 to 17 μ M, respectively. These results indicate that micromolar activities of ibogaine and the *O*-demethylated metabolite are relevant for defining binding site activities. At present, the metabolism and intracerebral disposition of ibogaine in the brain are not completely known. Both the parent drug and metabolite have high heptane/phosphate buffer partition coefficients,³² indicating their ability to penetrate the blood-brain barrier and consistent with a rapid entry of ibogaine into the brain. Partitioning of the parent drug into lipid may serve as a slow release storage 'depot'.³³ Sequestration of ibogaine into lipophilic compartments in brain, may result in lower concentrations of the parent drug in the extracellular fluid. The more polar nature of the desmethyl metabolite may result in higher extracellular fluid concentrations of the metabolite. If ibogaine is *O*-demethylated in brain, it is reasonable to conclude that the slow elimination of a central nervous system (CNS) trapped polar metabolite may contribute to some of the reported *aftereffects* of single oral dose administration of ibogaine in humans.

The receptor binding site profile of ibogaine suggests that multiple mechanisms of action may contribute to ibogaine's putative antiaddictive activity.^{34,27} Radioligand binding assays targeting 50 distinct neuroreceptors, ion channels and components of second messenger systems were used to establish a broad pharmacological profile for ibogaine. The results demonstrate that ibogaine interacts with a number of different molecular targets, including the mu and kappa opioid receptors and serotonin (5-HT)₂ and 5-HT₃, and muscarinic (M1 and M2) receptors, and monoamine uptake sites. In addition, ibogaine interacted with the *N*-methyl-D-aspartate (NMDA) receptor-coupled ion channel^{35,30} and sodium ion channel.³⁴ Ibogaine was inactive at γ -aminobutyric acid (GABA), benzodiazepine or chloride channel sites.³⁴ Many drugs acting on the CNS have pharmacological side effect profiles, which include weak actions at muscarinic receptors. Ibogaine has been shown to be a weak inhibitor at putative M1 and M2 sites.^{34,27} Ibogaine was inactive at brain/gut peptide receptors, prostaglandins, and second messenger binding sites.³⁴ Deecher *et al.*³⁶ had previously reported a similar ligand binding profile with an exception at 5-HT₂ sites. The lack of affinity of either ibogaine or noribogaine at 5-HT₂ (brain membranes) and 5-HT₆ and 5-HT₇ (recombinant proteins) sites has been confirmed in radioligand binding assays from our laboratory, suggesting further that the hallucinogenic activity of ibogaine (or the metabolite) is not mediated by an action at these 5-HT receptor subtypes. Ibogaine and noribogaine have affinities in the low micromolar range at the k₁ and k₂ opioid receptor subtypes.^{37,27} The potency of noribogaine at μ -opioid receptors labeled with [³H][D-Ala², MePhe⁴, Gly-

ol⁵]enkephalin ([³H]DAMGO was 200 nM.³⁸ These results suggest a more potent action for the metabolite than the parent drug at μ -opioid receptors.

The ability of ibogaine to inhibit [³H]MK-801 binding to the NMDA receptor complex^{35,34,39,40} may be of relevance to understanding the antiaddictive actions of ibogaine. MK-801 and the noncompetitive NMDA antagonist, ketamine, block the development of tolerance to the motor incoordinating actions of ethanol.^{41,42} MK-801 has been reported to block sensitization (reverse tolerance) to the behavioral activating effects of cocaine and amphetamine.^{43,44} The administration of MK-801 was shown to attenuate both the development of tolerance to the analgesic effect of morphine and morphine dependence.⁴⁵ Thus, ibogaine's ability to modify drug-seeking behavior may be due to a blockade of NMDA receptor-coupled cation channels. However, further studies are needed, since we have shown that the metabolite is less potent than ibogaine at inhibiting [³H]MK-801 binding in human brain preparations.³⁹ We have determined that ibogaine and its metabolite noribogaine are competitive antagonists at the MK-801 binding site in the NMDA-receptor cation channel. Both compounds competitively displaced specific [³H]MK-801 binding to caudate and cerebellar membranes from post-mortem human brain with submicromolar and micromolar affinities. In addition, ibogaine and noribogaine blocked the ability of NMDA to depolarize frog motoneurons in the isolated frog spinal cord.³⁹ The block of NMDA-depolarizations in frog motoneurons showed use-dependency and was very similar to the block produced by MK-801. In view of the abilities of MK-801 to affect the responses to addictive substances in preclinical investigations, our results are compatible with the idea that some of the antiaddictive properties of ibogaine may result from an interaction with NMDA-coupled cation channels. In this regard it is interesting to point out that there is considerable evidence to support the involvement of NMDA receptor stimulation in the behavioral sensitization to psychostimulants and opiates.⁴⁶ However, the lower potency of the *O*-demethylated metabolite in these assays may indicate that noribogaine does not have a significant interaction at NMDA receptor-coupled cation sites. Ibogaine's interaction with NMDA receptor-coupled cation channels may contribute to the psychotropic and high-dose neurotoxic actions of ibogaine.³⁴ Given the lower potency of the metabolite for inhibiting [³H]MK-801 binding, it is unlikely that the dwell time for noribogaine in the ion channel is additive to ibogaine's activity.

According to the model by Spanagel and Shippenberg,⁴⁷ opioids tonically regulate mesolimbic dopaminergic transmission through two opposing mechanisms that regulate dopamine release via actions at the cell body and terminal. Administration of the μ -opioid receptor agonist DAMGO into the nucleus accumbens and caudal ventral pallidum increases intracranial self-stimulation reward.⁴⁸ The selective k-1 agonist U-69593 attenuates cocaine-induced behavioral sensitization.⁴⁹ The nonselective k-opioid antagonist nor-binaltorphimine enhances morphine-induced sensitization.⁴⁷ Ibogaine decreased morphine self-administration²⁸ and inhibited some of the symptoms of naloxone-precipitated withdrawal in morphine-dependent rodents.^{14,11} Taken together, these observations suggest that opioid receptors may be involved in the inhibitory actions of ibogaine on opiate withdrawal and drug-taking behaviors. Ibogaine and noribogaine bind with micromolar or lower affinities at μ - and k-opioid receptor sites.^{34,27} Competition binding of ibogaine and [³H]naloxone in a sodium shift assay demonstrated a complex interaction, suggesting that ibogaine may recognize the high-affinity agonist state of the μ -opioid receptor.⁵⁰ However, ibogaine failed to modify morphine-induced antinociception in mice, while noribogaine potentiated morphine's antinociceptive response.⁵¹ Thus, the exact role of the parent drug or its active metabolite in ibogaine's inhibitory actions on morphine self-administration and the withdrawal syndrome remains unclear. The recent demonstration that noribogaine stimulated

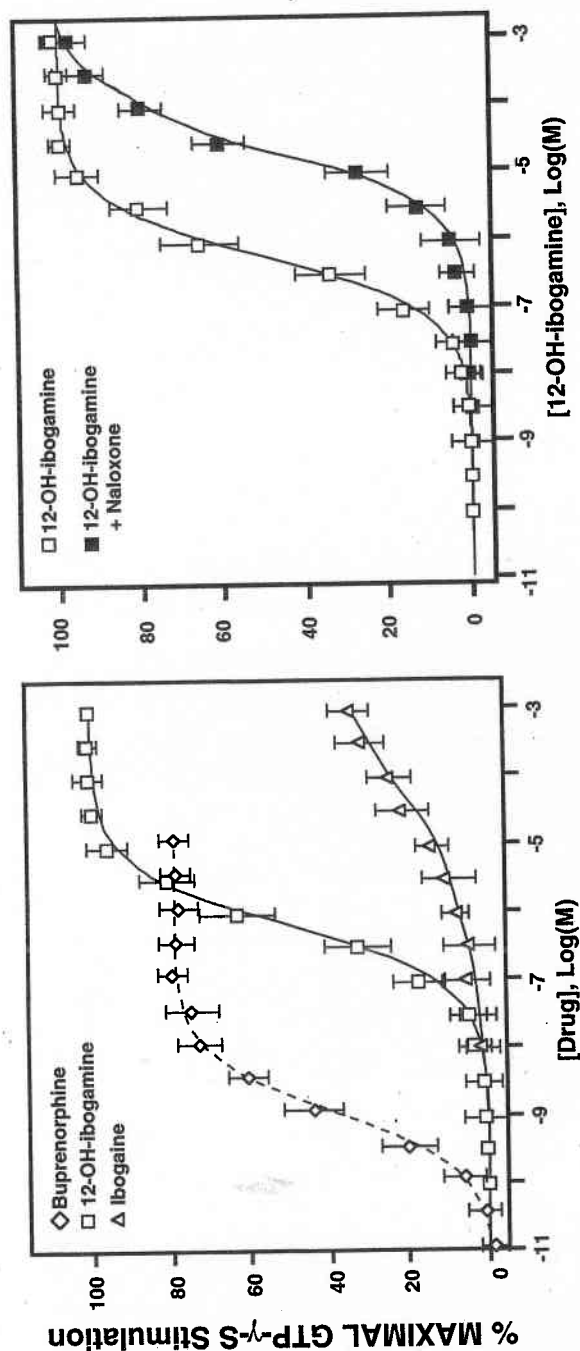


FIGURE 3. Stimulation of [35 S]GTP- γ -S binding to rat thalamic membranes by various concentrations of buprenorphine (partial agonist), noribogaine (12-OH-ibogaine) and ibogaine (*left panel*). Ibogaine failed to stimulate [35 S]GTP- γ -S binding over the same dose range. Data represent percentage of basal [35 S]GTP- γ -S binding measured in the presence of guanosine diphosphate (GDP) and absence of agonist. Effects of naloxone (0.1 μ M) on various concentrations of noribogaine in rat thalamic membranes (*right panel*). Values are means $\pm$ standard errors from three or more separate experiments performed in triplicate.

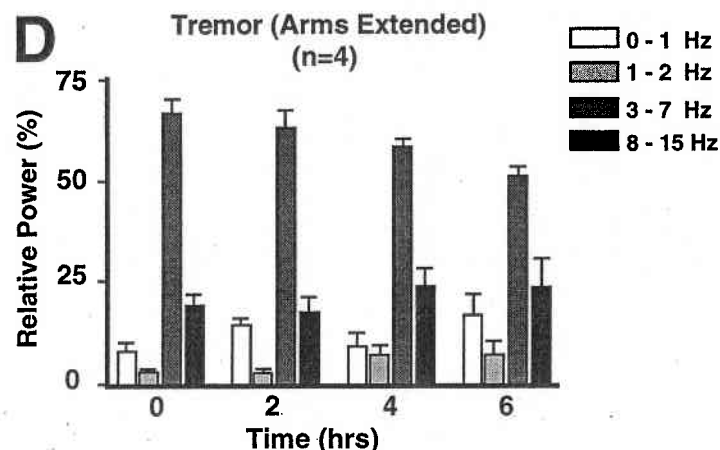
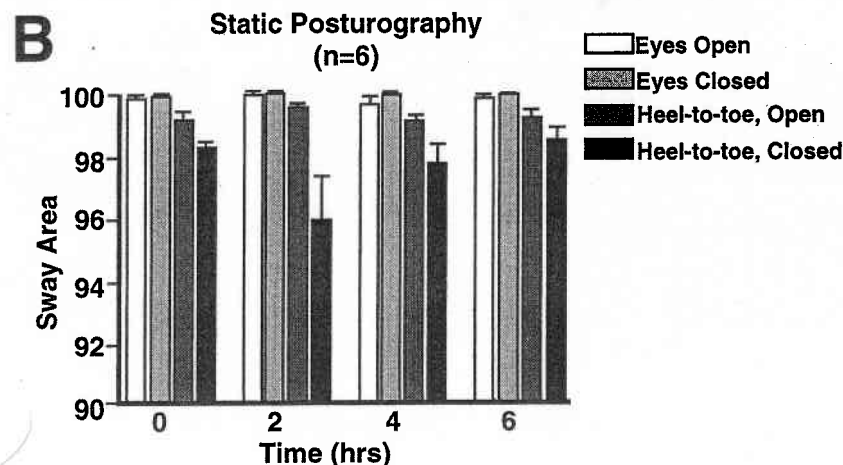
guanylyl-5'-(35 S)thio triphosphate (GTP- γ -S) binding to G proteins in a naloxone-sensitive manner indicates that the metabolite functions as a full μ -opioid agonist (FIG. 3). The functional response for noribogaine in rat thalamic membranes distinguished this compound from classic opiate drugs of differing intrinsic activities and binding site affinities.³⁸ The actions of noribogaine at μ -opioid receptors may account in part for the ability of ibogaine to reduce the symptoms of spontaneous withdrawal in opiate-dependent humans, since the long duration of action of noribogaine may produce a self-taper effect.³⁸

RATIONALE FOR IBOGAINE AS A PHARMACOTHERAPY OF DRUG DEPENDENCE

Clinical and preclinical investigations are determining how psychological symptoms associated with drug withdrawal, including depressed mood states and drug cravings, maintain chronic patterns of drug use.⁵² Chronic self-administration of cocaine and opiates results in a particularly intense euphoria and persistent drug dependence. Studies of cocaine and opiate dependence in animal models provide a rationale for pharmacotherapeutic agents with potential to attenuate withdrawal symptoms, to decrease drug craving, and to reduce relapse to previous patterns of drug use. The underlying assumption is that long-term substance abuse produces neurochemical adaptations in specific neural systems that regulate the capacity to experience pleasure (for review, see Ref. 53). Ibogaine may reestablish homeostasis in these neural systems, alleviating drug craving and diminishing the possibility for relapse to cocaine and opiate abuse.

Interventions with specific pharmacological agents should be guided by an understanding of the neurochemical derangements that underlie the clinical phases of drug abstinence.^{54,55} However, not enough is known about the spectrum of human neurochemical alterations occurring with chronic use of cocaine and opiates. Nevertheless, a rational approach to pharmacotherapy would include the development of agents to: a) initiate and facilitate the acute phase of abstinence, b) diminish drug-specific withdrawal symptoms, and c) prevent cue-associated relapse to previous patterns of drug-taking behavior. Such pharmacotherapeutic agents may include drugs that facilitate initiation of abstinence through limited dopaminergic agonist activity.⁵⁵ A medication that facilitates the first phase of abstinence by reversing the neurochemical alterations that are induced by chronic psychostimulant or opiate use would include also agents that possess neurochemical activity at a number of different neurotransmitter systems. For example, pharmacologic intervention would attempt to correct the dual deficit in dopamine and serotonin neurotransmission that has been postulated to underlie the anhedonia and depression associated with withdrawal from cocaine.^{56,57} The tendency to relapse to cocaine use that occurs during the early part of the 'crash' phase or during the later phases of withdrawal, could be treated with pharmacological agents to reduce drug craving.⁵⁸ Although drug craving is not easily quantified, the concept of craving is useful as a shorthand notation for all the external and internal cues that lead to drug-taking behavior.⁵³ The rationale for treatment of drug craving is based on the hypothesis that a dysregulation of neurotransmission of monoamines within the reward system is one of the causes of relapse. This change in brain function continues for months or years after the last use of the drug, and interacts with environmental factors such as social stress and situational triggers.⁵³

The discovery that ibogaine eliminates the signs and symptoms of opioid withdrawal and diminishes craving for opioids was made in the 1960s by a group of self-treating heroin addicts.⁵⁹ A single oral dose administration of ibogaine (6 mg/kg to 19 mg/kg) was associated with a disruption of five addicts' use of opiates for up to six



phy with a portable bedside computerized platform was used to quantify body sway while standing normally and in a heel-to-toe position with eyes opened and eyes closed. Measurements were taken at baseline and every two hours following oral administrations of ibogaine. Dynamic posturography measured functional limits of stability over 6 hr. Accelerometry was used to measure tremor of the hands at rest and with arms extended over the same time period. Whole body tremor, akinesia, and retropulsion were measured with the Neurotest™ apparatus at baseline and 48 hr after drug administration. Both doses of ibogaine produced no clinically visible effects, but static posturography revealed a trend (albeit not significant) toward increased body sway when subjects stood in the heel-to-toe posture with eyes closed. Dynamic posturography and the Neurotest measurements revealed no changes from baseline. Hand accelerometry did

not show any effects of ibogaine on tremor (at rest or with arms extended). However, baseline measurements of tremor revealed quantitative differences between cocaine-dependent patients and age-matched and drug-free control subjects. Power spectrum analysis of these data revealed an increase in the 3–7-Hz range, supporting the hypothesis that early cocaine abstinence may reflect a hypodopaminergic state.⁶⁴ Similar observations on patients receiving oral doses of ibogaine in a range of 10 to 30 mg/kg in offshore clinical settings, failed to demonstrate any effects with Neurotest measurements taken at 5 to 7 days post dose ($n = 10$; 8 male, 2 female; data not shown). In addition to the lack of posturographic abnormalities, clinical neurologic exams demonstrated no evidence of permanent cerebellar ataxia in these subjects.

Our research group had the opportunity to conduct a neuropathological evaluation on a female subject who had received 4 doses of ibogaine ranging from 10 to 30 mg kg⁻¹ over a period of 15 months. The last two administrations occurred in a Panamanian hospital, approximately 25 days prior to her death from natural causes. Before receiving these last ibogaine treatments, the subject received a series of clinical evaluations at the University of Miami School of Medicine. Her diagnoses at that time included: 1) opiate and cocaine dependence; 2) amenorrhea for 11 months; 3) a history of asthma; 4) a history of peptic ulcer disease; and 5) a history of hypertension. The general physical exam was normal. Neurological examination (including magnetic resonance imaging (MRI), electroencephalogram (EEG) and a Neurotest gait analysis for cerebellar signs were normal. Urine toxicology was positive for cocaine, opiates, and marijuana. She received two doses of ibogaine three days apart (10 mg/kg and 20 mg/kg). Approximately one week later, she returned to Miami for follow-up neurological evaluations. At that time, the patient was admitted to the hospital for the evaluation of tremors. The examination revealed temperature 98, pulse 92, respirations 22, and blood pressure 160/108. General physical exam was notable for “an ulcerative lesion on her right anterior thigh with 3 to 4 cm erythematous area surrounding it and partially healed.” Repeat neurological exam at that time was grossly normal. She was treated with clonidine and discharged. The patient went back to New York where she was treated with diazepam for anxiety and poor sleep. She returned to Miami three weeks later, where she complained to a friend that she had been having diarrhea and vomiting since eating raw fish the previous night. Her vomiting progressively worsened, but she did not seek medical attention. The subject died thereafter and was autopsied. The toxicology screen was positive for benzodiazepines only. Postmortem antinuclear antibody (ANA) and rheumatoid factor were negative. The postmortem autopsy revealed mesenteric artery thrombosis with small bowel infarction as the cause of death, left renal cortical hemorrhagic infarcts, splenic infarct, a capsular hemorrhage of the right ovary, and agonal aspiration of gastric contents. Comprehensive evaluations of the histopathology revealed multiple microscopic arterial thrombi in several tissues, although there was no evidence of arteritis whatsoever. These observations led to the conclusion that the pathological picture was that of a generalized hypercoagulable state. The pathological picture was most consistent with an infectious source (the leg ulcer) producing a thrombotic process resulting in mesenteric artery occlusion and death. This cause of death was more likely than an acute drug toxicity (which would have occurred at 25 days after ibogaine administration).

Neuropathological evaluation revealed slight medullary neuroaxonal dystrophy and an old focal meningeal fibrosis. There were no degenerative changes seen in the cerebellum; cerebellar Purkinje cells were normal and there was no evidence of any significant cytopathology or neurodegeneration in any other brain area (Fig. 5). There was no evidence of astrocytosis or microglial activation. The neuropathological analysis for a human subject (NH) was important in light of the observations of O’Hearn and Molliver,⁶¹ which demonstrated that at high doses, ibogaine administrations result in the

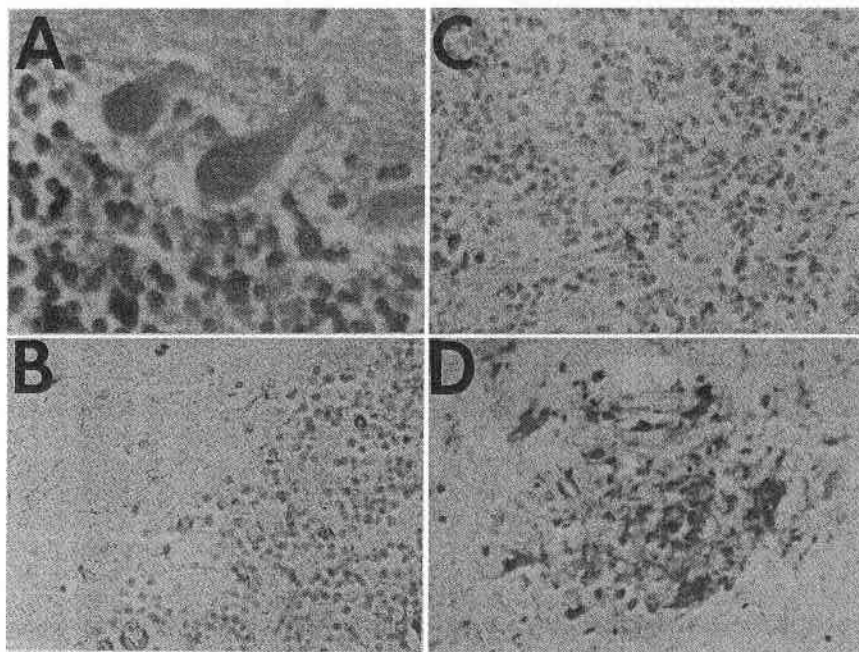


FIGURE 5. Postmortem neuropathological examination of the cerebellum from a female subject who had received four ibogaine treatments. (A) Section taken at the level of the anterior vermis. Note the normal cytoarchitecture of the cerebellar Purkinje cells. (B) Near adjacent section stained with an anti-ferritin antibody to reveal the presence of microglial cells. There is evidence of a small number of faintly stained microglial cells. (C) Near adjacent section labeled with a ricin A (RCA) lectin antibody to localize resting and activated microglia. A few scattered microglial cells are observed in the molecular cell layer. These appear to be in a resting state. (D) A positive control section taken from an HIV-infected brain shows robust staining of a microglial nodule for comparison.

degeneration of cerebellar Purkinje cells in rats.' At a National Institute on Drug Abuse (NIDA)/Medical Development Division (MDD)/MDD Ibogaine Review Meeting, these investigators reported findings that the toxicity in monkeys was much less than in rats.⁶² Our own studies conducted in African green monkeys (vervets) with routine histopathological evaluation (independently rated by two neuropathologists) failed to demonstrate any neuropathological damage caused by ibogaine following 5 days of repeat dosing at either 25 mg/kg p.o. or 100 mg/kg s.c.⁶⁰ Taken together, these results demonstrate further that the risk for cerebellar toxicity in human subjects in the dose range purported to be effective for opiate and cocaine detoxification is low.

FUTURE DIRECTIONS

The two major forms of treatment for drug abuse, psychotherapy and pharmacotherapy, have tended to develop along parallel but separate lines.¹⁰ Ibogaine is an interesting example of a pharmacotherapeutic strategy that has the added benefit of it

being an adjuvant to psychotherapy. While much more clinical research is needed, ibogaine has shown preliminary efficacy for the management of opiate detoxification and for short-term stabilization and maintenance of drug users as they prepare to enter treatment. Ibogaine seems to have an added benefit in that it helps clients to establish their resolve to stop substance misuse and to gain self-control over their destructive behaviors. We have observed in offshore studies that ambivalent clients become motivated to seek long-term treatment, since the ibogaine experience seems to bolster the patient's own motivational resources for change.

Drug dependence results from distinct, but interrelated neurochemical adaptations, which underlie tolerance, sensitization and withdrawal. Ibogaine's ability to alter drug-taking behavior may be due to combined actions of either the parent drug and/or its active metabolite at key pharmacological targets that modulate the activity of dopaminergic circuits.^{27,38} The active metabolite noribogaine has a unique spectrum of activities as compared to the parent compound. Recent studies have suggested that noribogaine's efficacy as a full μ -opioid agonist may explain ibogaine's ability to block the acute signs of opiate withdrawal and its suppressive effects on morphine self-administration.³⁸ In addition, a preclinical evaluation of noribogaine's anticocaine medication effects has been conducted in rat models. These results demonstrated that noribogaine antagonized cocaine-induced locomotor stimulation and reinforcement.³¹ Ibogaine's interaction with NMDA receptor-coupled cation channels may contribute to the adverse effects of the drug, including the psychotropic (phencyclidine hydrochloride (PCP)-like actions) and the high-dose neurotoxic changes in cerebellar Purkinje cells.³⁴ Given the lower potency of the metabolite at this molecular target, it is likely that the channel activity of ibogaine may partly explain ibogaine's acute effects. Since ibogaine is cleared rapidly after oral administration, the observed *aftereffects* of ibogaine treatments on drug craving, mood and cognition may be related to the targeted actions of the metabolite noribogaine. The potential development of a slow release formulation of noribogaine as an anticraving medication for opiates and psychostimulants deserves further consideration.

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REFERENCES

1. BARABE, P. 1982. La religion d'Eboga ou le Bwite de Fangs. *Med. Trop.* **12**: 251-257.
2. POPIK, P., R.T. LAYER & P. SHOLNICK. 1995. 100 Years of ibogaine: Neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol. Rev.* **47**: 235-253.
3. HOFFER, A. & H. OSMOND. 1967. *The Hallucinogens*. Academic Press, New York.
4. POUCHET, G. & J. CHEVALIER. 1905. Les nouveaux remèdes. Sur l'action pharmacodynamique de l'ibogaine. *Bull. Gen. Ther.* **149**: 211.
5. LAMBERT, M. & E. HECKEL. 1901. Sur la racine d'iboga et sur l'ibogaine. *Compt. Rend.* **133**: 1236.
6. PHISALIX, M.C. 1901. Action physiologique de l'ibogaine. *Compt. Rend. Soc. Biol.* **53**: 1077.

7. GOUTAREL, R., O. GOLLNHOFFER & R. SILLANS. 1991. Pharmacodynamics and therapeutic applications of iboga and ibogaine. *Psychedel. Monogr. Essays* 6: 71-111.
8. LOTSOFF, H.S. 1995. Ibogaine in the treatment of chemical dependency disorders: Clinical perspectives. *Multidiscip. Assoc. Psychedel. Stud.* 5: 16-27.
9. SISCO, B. 1993. Interrupting drug dependency with ibogaine: A summary of four case histories. *Multidiscip. Assoc. Psychedel. Stud.* 4: 15-24.
10. CARROLL, K.M. 1997. Integrating psychotherapy and pharmacotherapy to improve drug abuse outcomes. *Addic. Behav.* 22: 233-245.
11. GLICK, S.D., K. ROSSMAN, N.C. RAO, I.M. MAISONNEUVE & J.N. CARLSON. 1992. Effects of ibogaine on acute signs of morphine withdrawal in rats: Independence from tremor. *Neuropharmacology* 31: 497-500.
12. GLICK, S.D., M.E. KUEHNE, J. RAUCCI, T.E. WILSON, D. LARSON, R.W. KELLER & N.J. CARLSON. 1994. Effects of *iboga* alkaloids on morphine and cocaine self-administration in rats: Relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. *Brain Res.* 657: 14-22.
13. MAISONNEUVE, I.M. & S.D. GLICK. 1992. Interactions between ibogaine and cocaine in rats: *In vivo* microdialysis and motor behavior. *Eur. J. Pharmacol.* 212: 263-266.
14. DZOLJIC, E.D., C.D. KAPLAN & M.R. DZOLJIC. 1988. Effect of ibogaine on naloxone-precipitated withdrawal syndrome in chronic morphine dependent rats. *Arch. Int. Pharmacodyn. Ther.* 294: 64-70.
15. ACETO, M.D., E.R. BOWMAN & L.S. HARRIS. 1990. Dependence studies of new compounds in the rhesus monkey, rat and mouse. *NIDA Res. Monogr.* 95: 578.
16. SHARPE, L.G. & J.H. JAFFE. 1990. Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine-dependent rat. *Neuroreport* 1: 17-19.
17. LUXTON, T.L., L.A. PARKER & S. SIEGEL. 1994. Effect of ibogaine on morphine and naloxone-induced place conditioning. *Soc. Neurosci. Abstr.* 20: 502.11.
18. SORER, H. 1995. Pharmacological summary of ibogaine. Presented to the NIDA-Sponsored Ibogaine Review Meeting, March 1995.
19. SERSHEN, H., A. HASHIM, L. HARSING & A. LAJTHA. 1992. Ibogaine antagonizes cocaine-induced locomotor stimulation in mice. *Life Sci.* 50: 1079-1086.
20. MAISONNEUVE, I.M., K.L. ROSSMAN, R.W. KELLER, JR. & S.D. GLICK. 1992. Acute and prolonged effects of ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats. *Brain Res.* 575: 69-73.
21. SERSHEN, H., A. HASHIM & A. LAJTHA. 1994. Ibogaine reduces preference for cocaine consumption in C57BL/6 mice. *Pharmacol. Biochem. Behav.* 47: 13-19.
22. CAPPENDIX, S.L.T. & M.R. DZOLJIC. 1993. Inhibitory effects of ibogaine on cocaine self-administration in rats. *Eur. J. Pharmacol.* 241: 261-265.
23. DWORKIN, S.I., S. GLEESON, D. MELON, T.R. LOVES & T.J. MARTIN. 1995. Effects of ibogaine on responding maintained by food, cocaine, and heroin reinforcement in rats. *Psychopharmacology* 117: 257-261.
24. MANSBACH, R.S., R.L. BALSTER, M. GREGORY & E. SOENGHEN. 1988. Effects of ibogaine pretreatment on IV cocaine self-administration in rhesus monkey. *NIDA Contract Report SA 92.16, NIDA Contract 271-8156, Pharmacological and Toxicological Evaluation of Treatment Drugs.*
25. SCHECTER, M.D. & T.L. GORDON. 1993. Comparison of the behavioral effects of ibogaine from three sources: Mediation of discriminative activity. *Eur. J. Pharmacol.* 249: 79-84.
26. HEARN, W. L., D.C. MASH, J. PABLO, G. HIME, N.C. SAMBOL & F.M. DOEPFEL. 1995. Pharmacokinetics of ibogaine: Analytical method, animal-human comparisons, and the identification of a primary metabolite. *Proceedings of the TIAFT-SOFT Joint Congress*, Oct. 21-Nov. 4, 1994. V. Spiehl, Ed.: 325-334. *Omnipress. Ann Arbor, MI.*
27. STALEY, J.K., Q. OUYANG, J. PABLO, W.L. HEARN, D.D. FLYNN, R.B. ROTHMAN, K.C. RICE & D.C. MASH. 1996. Pharmacological screen for activities of 12-hydroxyibogamine: A primary metabolite of the indole alkaloid ibogaine. *Psychopharmacology* 127: 10-18.
28. GLICK, S.D., K. ROSSMAN, S. STEINDORF, I.M. MAISONNEUVE & J.N. CARLSON. 1991. Effects and aftereffects of ibogaine on morphine self-administration in rats. *Eur. J. Pharmacol.* 195(3): 341-345.
29. HEARN, W. L., J. PABLO, G. HIME & D.C. MASH. 1995. Identification and quantitation of

- ibogaine and an *o*-demethylated metabolite in brain and biological fluids using gas chromatography/mass spectrometry. *J. Anal. Toxicol.* 19: 427-434.
30. MASH, D.C., J.K. STALEY, M.H. BAUMANN, R.B. ROTHMAN & W.L. HEARN. 1995. Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin. *Life Sci.* 57: PL45-PL50.
- 31a. SCHENK, S., B. PARTRIDGE, B. HARWELL, J. PABLO & D.C. MASH. 1998. Preclinical screening of an ibogaine metabolite (noribogaine) on cocaine-induced hyperlocomotion and cocaine self-administration. *Psychopharmacology*. Under review/revision.
- 31b. MASH, D.C. & S. SCHENK. 1996. Preclinical screening of an ibogaine metabolite (noribogaine) on cocaine-induced hyperlocomotion and cocaine self-administration. *Soc. Neurosci. Abstr.* 22: 1929.
32. ZETTLER, G., G. SINGBARTL & L. SCHLOSSER. 1972. Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids. *Pharmacology* 7: 237-248.
33. HOUGH, L.B., S.M. PEARL & S.D. GLICK. 1996. Tissue distribution of ibogaine after intraperitoneal and subcutaneous administration. *Life Sci.* 58: PL119-PL122.
34. SWEETNAM, P.M., J. LANCASTER, A. SNOWMAN, J.L. COLLINS, S. PERSCHKE, C. BAUER & J. FERKANY. 1995. Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity. *Psychopharmacology* 118: 369-376.
35. POPIK, P., R.T. LAYER & P. SKOLNICK. 1994. The putative anti-addictive drug ibogaine is competitive inhibitor of [³H]MK-801 binding to the NMDA receptor complex. *Psychopharmacology* 114: 672-674.
36. DEECHE, D.C., M. TEITLER, D.M. SODERLUND, W.G. BORNHANN, M.E. KUEHNE & S.D. GLICK. 1992. Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies. *Brain Res.* 57: 242-247.
37. PEARL, S.M., K. HERRICK-DAVIS, M. TEITLER & S.D. GLICK. 1995. Radioligand-binding study of noribogaine, a likely metabolite of ibogaine. *Brain Res.* 675: 342-344.
38. PABLO, J. & D.C. MASH. 1998. Noribogaine stimulates naloxone-sensitive [³⁵S]GTPγS binding. *Neuroreport* 9: 109-114.
39. MASH, D.C., J. PABLO, J. K. STALEY, A.M. HOLOHEAN, J.C. HACKMAN & R.A. DAVIDOFF. 1995. Properties of ibogaine and a principal metabolite (12-hydroxyibogamine) at the MK-801 binding site on the NMDA-receptor complex. *Neurosci. Lett.* 192: 53-56.
40. GLICK, S.D., I.M. MAISONNEUVE & S.M. PEARL. 1996. Evidence for roles of κ-opioid and NMDA receptors in the mechanisms of action of ibogaine. *Brain Res.* 749: 340-343.
41. KHANNA, J.M., H. KALANT, G. SHAH & A. CHAU. 1993. Effect of D-cycloserine on rapid tolerance to ethanol. *Pharmacol. Biochem. Behav.* 45(4): 983-986.
42. WU, P.H., S.J. MICHIC, J.F. LIU, A. DZUNG LE & H. KALANT. 1993. Blockade of chronic tolerance to ethanol by the NMDA antagonist, (+)-MK-801. *Eur. J. Pharmacol.* 231: 157-164.
43. KARLER, R., L.D. CALDER, I.A. CHAUDHRY & S.A. TURKANIS. 1989. Blockade of 'reverse tolerance' to cocaine and amphetamine by MK-801. *Life Sci.* 45: 500-606.
44. PUDIACK, C.M. & M.A. BOZARTH. 1993. L-NAME and MK-801 attenuate sensitization to the locomotor-stimulating effect of cocaine. *Life Sci.* 53(20): 1517-1524.
45. TRUJILLO, K.A., & H. AKIL. 1991. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science* 251: 85-87.
46. TRUJILLO, K.A. & H. AKIL. 1995. Excitatory amino acids and drugs of abuse: A role for N-methyl-D-aspartate receptors in drug tolerance, sensitization and physical dependence. *Drug Alcohol Depend.* 38: 139-154.
47. SPANAGEL, R., A. HERZ & T.S. SHIPPENBERG. 1992. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. *Proc. Natl. Acad. Sci. USA* 89: 2046-2050.
48. JOHNSON, P.L., J.R. STELLAR & D.A. PAUL. 1993. Regional reward differences within the ventral pallidum are revealed by microinjections of a mu opiate receptor agonist. *Neuropharmacology* 32: 1305-1314.
49. HEIDREDER, C.A., S.R. GOLDBERG & T.S. SHIPPENBERG. 1993. The kappa opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization in the rat. *Brain Res.* 616: 335-338.

50. CODD, E.E. 1995. High affinity ibogaine binding to a mu opioid agonist site. *Life Sci.* **57**(20): PL315-PL320.
51. BHARGAVA, H.N., Y.J. CAO & G.M. ZHAO. 1997. Effects of ibogaine and noribogaine on the antinociceptive action of μ -, δ -, and κ -opioid receptor agonists in mice. *Brain Res.* **752**: 234-238.
52. GAWIN, F.H. 1991. Cocaine addiction: Psychology and neurophysiology. *Science* **251**: 1580-1586.
53. O'BRIEN, C.P. 1997. A range of research-based pharmacotherapies for addiction. *Science* **278**: 66-69.
54. DACKIS, C.A. & M.S. GOLD. 1985. Pharmacological approaches to cocaine addiction. *J Subst. Abuse Treat.* **2**: 139-145.
55. GAWIN, F.H. & E.H. ELLINWOOD. 1988. Cocaine and other stimulants: Actions, abuse and treatment. *N. Engl. J. Med.* **318**: 1173-1182.
56. ROBERTSON, M.W., C.A. LESLIE & J.P. BENNETT. 1991. Apparent synaptic dopamine deficiency induced by withdrawal from chronic cocaine treatment. *Brain Res.* **538**: 337-339.
57. BAUMAN, M.H. & R.B. ROTHMAN. 1997. Serotonergic dysfunction during cocaine withdrawal: implications for cocaine-induced depression. In *Drug Abuse Handbook*. S. Karch, Ed.: 463-484. CRC Press. Boca Raton.
58. JAFFE, J.H., N.G. CASCELLAR, K.M. KUMOR & M.A. SHERER. 1989. Cocaine-induced cocaine craving. *Psychopharmacology* **97**: 59-64.
59. SHEPARD, S.G. 1994. A preliminary investigation of ibogaine: Case reports and recommendations for further study. *J Subst. Abuse Treat.* **11**(4): 379-385.
60. MASH, D.C. 1995. Preclinical studies of ibogaine in the primate: Anatomical, neurochemical and behavioral observations. Presented to the NIDA-Sponsored Ibogaine Review Meeting, March 1995.
61. O'HEARN, E. & M.E. MOLLIVER. 1993. Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline. *Neuroscience* **55**: 303-310.
62. TOUCHETTE, N. 1993. Ibogaine neurotoxicity raises new questions in addiction research. *J. NIH Res.* **5**: 50-55.
63. MOLINARI, H.H., I.M. MAISONNEUVE & S.D. GLICK. 1996. Ibogaine neurotoxicity: A reevaluation. *Brain Res.* **737**: 255-262.
64. SANCHEZ-RAMOS, J.R., L. RAYMON, C. KOVERA & D.C. MASH. 1997. The effect of ibogaine on tremor and balance in cocaine-dependent patient volunteers. *NIDA Monogr. Ser.* **174**: 215.

Prenatal Cocaine Exposure Affects Postnatal Dopaminergic Systems in Various Regions of the Rat Brain^a

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ABSTRACT: Pregnant female Sprague-Dawley rats were injected once daily with either 40 mg/kg cocaine hydrochloride or 0.9% saline from gestation day (GD)12 to GD 21. On postnatal day (PND)30, male offspring were sacrificed and fresh tissue from the striatum (ST) and nucleus accumbens (NA) was dissected for assessment of dopamine (DA) receptor affinity, DA uptake and DA release. 10^{-6} M cocaine inhibited [3 H]-DA uptake in ST tissue, whereas 10^{-4} and 10^{-5} M cocaine inhibited [3 H]-DA uptake in the NA tissue of postnatally exposed cocaine offspring versus saline-treated controls ($p < 0.05$). DA release stimulated by 10^{-6} M amphetamine was significantly reduced in both the ST ($p < 0.001$) and NA ($p < 0.01$) of postnatal offspring exposed to cocaine in utero compared with saline controls. In utero cocaine exposure did not influence offspring ST or NA dopamine 1 (D_1) dissociation constant (K_d) or receptor density (B_{max}). However, the treatment group experienced a significant increase of binding affinity for the ST D_2 receptor with no change in D_2 B_{max} . The treatment group also experienced no change in D_2 receptor binding affinity or number of binding sites in the NA. These results show that in utero exposure to cocaine results in altered postnatal dopaminergic function.

INTRODUCTION

Over the past decade, there has been an increase in substance abuse during pregnancy.^{1,2} Exposure to cocaine during pregnancy has been reported to cause altered dopaminergic function in offspring.^{3,4} Offspring exposed to cocaine in utero exhibit enhanced striatum (ST) dopamine 1 (D_1) receptor binding,⁴ enhanced D_1 receptor binding,⁵⁻⁷ decreased ST dopamine transporter (DAT) activity⁸ and a decreased number of spontaneously active dopaminergic neurons in the substantia nigra and ventral tegmental area.^{9,10} Postnatal abnormalities in central dopaminergic activity may contribute to the enhanced behavioral sensitization to cocaine,¹¹ enhanced stress perception^{12,13} and diminished selective attention and learning,^{14,15} which are characteristic to cocaine-exposed offspring. The present investigation attempts to examine for alterations of various aspects of dopaminergic function in offspring exposed to cocaine in utero.

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